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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,509	01/03/2002	Terry J. Smith	P-HR 5214	5468

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/038,509	SMITH ET AL.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 are pending.

2. Applicant's election, with traverse of claims 1-8 and the species of Graves' disease in claim1, in the reply filed on 01/09/2007 is acknowledged.

Applicant's traversal is on the ground that the groups are classified in the same class and subclass and that a thorough search of the elected method of Group I is likely to result in art relevant to examination on the method of Group II.

This is not found persuasive because a prior art search also requires a literature search. In addition, the inventions of Group I and II are distinct because the patient populations are distinct. A prior art search of IgG and IGF-1 in Graves' disease will not bring up references that cover rheumatoid arthritis unless the reference covers both diseases. Given the complex pathology to both diseases, it is in the very least, not common to study two disease pathologies in a single reference. Therefore, a search of rheumatoid arthritis and Graves' disease requires twice as much search time as a search for Graves disease references alone. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-8 are currently under examination as they read on a method of detecting Graves disease in a patient comprising obtaining a biological sample from the patient and measuring the binding of disease specific IgG with IGF-1 relative to a control wherein an elevated level of IgG IgF-1 binding relative to the control indicates Graves disease.

4. Page 1, line one of the specification should be amended top update the status of application 10/,046,651, now U.S. Patent 6,936,426

Claim Objections

5. Claims 1 and 5 are objected to because of the following informalities:

Claim 1 recites 'biding' and it appears that it should be the word 'binding'; and Claim 5 recites 'IC-16' and it appears that it should be the word 'IL-16.' Claim 8 lacks an 'and' between ascites and tissues for proper Markush group claim form. .Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. Claim 1 does not recite a contact step for IgG that is contacted with IGF-1 nor does it recite a detection step to measure the bound IgG/IGF-1. Claims 2, 3 and 6 do not recite any contact or detection steps to determine T cell activation by measuring markers or migration. It is unclear how the methods are performed. Claims 2-6 do not recite correlation steps. It is unclear how the markers recited in 3-5 relate to T cell activation and it is also unclear how T cell activation relates to disease. For example, is the lack or the presence of IL-16 a measure of T cell activation? In either case, how does IL-16/ RANTES expressed by an activated T cell relate to IgG/IGF-1 binding? In the same way, how does T cell migration relate to IgG/IGF-1 binding? The claims are unclear as to how determinations are being made about T cell activation with relation to marker expression, migration and, in turn, IgG/ IGF-1 binding.

Further, claim 1 recites 'obtaining a biological sample' from a patient, but it does not recite that the disease specific IgG is contained within that sample. Claims 2-6 require T cells to perform the methods, but it unclear as to the source of the T cells. What is present in the biological sample?

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

A method of detecting Graves disease or rheumatoid arthritis in a patient comprising obtaining **a biological sample** from the patient and measuring the binding of disease specific IgG with **IGF-1** relative to a control wherein an elevated level of **IgG IGF-1** binding relative to the control indicates Graves disease or rheumatoid arthritis of claim 1; wherein the measuring step is **a determination of T-cell activation** of claim 2, wherein the **determination measures a chemical marker expressed by activated T cells** of claim 3; wherein the marker is RANTES of claim 4; wherein the marker is IL-16 of claim 5; wherein the **determination is T-cell migration** of claim 6; wherein the patient is human of claim 7; and wherein the biological samples is selected from a group consisting of: blood, urine, synovial fluid, ascites and tissues of claim 8.

The specification does not disclose a method of detecting Graves disease or rheumatoid arthritis comprising measuring the binding of disease specific IgG with IGF-1. Throughout the specification it is disclosed that **IGF-1 receptor** binds disease-specific IgG, not IGF-1 itself. For example, on page 13, the specification discloses that "other aspects of the present invention are diagnostic methods to determine whether a patient exhibits disease-specific antibody-activated fibroblasts" including "detecting the activation of lymphocyte via IgG-mediated activation of T cells through the IGF-1 receptor." On pages 14, line 1, the specification discloses that "the diagnostic utility of the invention is based in part on the ability to correlate disease-specific IgG with activated T cell and the identification of the IGF-1 receptor as the disease target." In addition, "one advantage of this diagnostic embodiment is an expansion of the cell type that may be used to measure the interaction of IgG in a patient sample with the IGF-1

receptor." The art confirms the interaction of IgG from both Graves disease and rheumatoid arthritis patients with the IGF-1 receptor in Pritchard et al. (PTO-892, Reference U, whoel document, abstract in particular). The reference teaches that fibroblasts from Graves disease patients are activated by IgGs obtained from the same donors to synthesize and release IL-16 and RANTES and that the induction is mediated through insulin-like growth factor-1 receptor (IGF-1R). The reference also teaches that fibroblasts from rheumatoid arthritis patients are activated by IgGs from the same donors to synthesize and release IL-16 and RANTES and that the induction is mediated through IGF-1R. Upon engagement of IgG with IGF-1R on the fibroblasts of both Graves' disease and RA patients, the fibroblasts are induced to express chemoattractants that may induce migration into sites of inflammation that are associated with both diseases. Therefore, applicants do not disclose, nor does the art support, a method of detecting Graves disease or rheumatoid arthritis comprising measuring the binding of disease specific IgG with IGF-1.

The term 'biological sample' in claim 1 encompasses any biological sample from any source, including sources that do not contain antibodies or fibroblasts. The art is highly unpredictable with regard to obtaining IgG and/ or fibroblasts from all biological sample sources.

The term "determination of T-cell activation" is extremely broad and encompasses both the expression and down-regulation of any cell surface marker, cytokine, protein, DNA, RNA or other factor associated with the stimulation of a particular T cell, including as yet undiscovered proteins and factors. This term is extremely broad and covers markers that are upregulated in

one type of T cell activation and down-regulated in another type of T cell activation. For example, the cytokine profiles and function of CD8+ (Tc1 and Tc2) and CD4 + (Th1 and Th2) T cells are all distinct as taught by Woodland et al. (PTO-892, Reference V, entire document; page 336-7 in particular). Therefore, the recitation of determining "T cell activation" to diagnose disease is not supported by the disclosure.

Further, the specification does not support the recitation of measuring "a chemical marker expressed by activated T cells", including IL-16 and RANTES. Rather, as disclosed on pages 33-37 and 39-40, the IgG antibodies of Graves patients are used to stimulate the IGF-1 receptor on fibroblasts. The fibroblasts produce IL-16 and RANTES, which may attract T cells because the cytokines have chemoattractive properties. The specification discloses measuring IL-16 and RANTES from fibroblasts. Disease-specific IgG stimulation of the IGF-1 receptor on fibroblasts induces increased expression of IL-16 and RANTES. Therefore, increased levels of IL-16 and RANTES indicates the presence of Graves disease specific IgG. Another method whereby the specification discloses determining the presence of disease-specific IgG follows the same logic. That method measures the amount of "T cell migration" as an indicator of the quantity of RANTES and IL-16, which, in turn, is an indicator of the presence of disease-specific IgG. Therefore, the positive demonstration of T cell migration toward antibody stimulated fibroblasts is an indicator of disease.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working

examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method of detecting Graves disease or rheumatoid arthritis in a human patient comprising contacting an antibody sample with a fibroblast sample from the same patient and measuring the IL-16 and/or RANTES levels that are induced by the diseas-specific IgG activation of the IGF-1R on the fibroblast, whereby increased expression of either cytokine is associated with the presence of disease specific IgG and is an indicator of disease; and a method of detecting Graves disease or rheumatoid arthritis in a human patient comprising: contacting an antibody sample with a fibroblast sample from the same patient; exposing a NWNA-T cell to the activated fibroblast using a Boyden chamber; measuring the T cell migration toward the activated fibroblast, and determining that positive T cell migration indicates IL-16 and/or RANTES expression in disease-specific IgG-activated fibroblasts through their IGF-1R, whereby increased expression of either cytokine is associated with the presence of disease specific IgG.

Applicant is not in possession of: A method of detecting Graves disease or rheumatoid arthritis in a patient comprising obtaining **a biological sample** from the patient and measuring the binding of disease specific IgG with **IGF-1** relative to a control wherein an elevated level of **IgG IGF-1** binding relative to the control indicates Graves disease or rheumatoid arthritis of claim 1; wherein the measuring step is a **determination of T-cell activation** of claim 2, wherein the determination measures **a chemical marker expressed by activated T cells** of claim 3; wherein the marker is RANTES of claim 4; wherein the marker is IL-16 of claim 5; wherein the determination is T-cell migration of claim 6; wherein the patient is human of claim 7; and wherein the biological samples is selected from a group consisting of: blood, urine, synovial fluid, ascites and tissues of claim 8.

The specification does not disclose a method of detecting Graves disease or rheumatoid arthritis comprising measuring the binding of disease specific IgG with IGF-1. Throughout the specification it is disclosed that IGF-1 receptor binds disease-specific IgG, not IGF-1 itself. For example, on page 13, the specification discloses that "other aspects of the present invention are diagnostic methods to determine whether a patient exhibits disease-specific antibody-activated fibroblasts" including "detecting the activation of lymphocyte via IgG-mediated activation of T cells through the IGF-1 receptor." On pages 14, line 1, the specification discloses that "the diagnostic utility of the invention is based in part on the ability to correlate disease-specific IgG with activated T cell and the identification of the IGF-1 receptor as the disease target." In addition, "one advantage of this diagnostic embodiment is an expansion of the cell type that may be used to measure the interaction of IgG in a patient sample with the IGF-1 receptor."

Therefore, the recitation of IGF-1 is not sufficient given the lack of examples and support in the specification to support the recited term, as well as the presence of evidence to the contrary in the specification.

The term 'biological sample' in claim 1 encompasses any biological sample from any source, including sources that do not contain antibodies or fibroblasts. The specification described the use of orbital fibroblasts and serum. The specification does not provide sufficient support for the recited genus term 'biological sample.'

The term "determination of T-cell activation" is extremely broad and encompasses both the expression and down-regulation of any cell surface marker, cytokine, protein, DNA, RNA or other factor associated with the stimulation of a particular T cell, including as yet undiscovered proteins and factors. It also includes the determination of T cell activation by any method, including as yet unknown methods. There is insufficient description in the specification to support the recited term.

Further, the specification does not support the recitation of measuring "a chemical marker expressed by activated T cells. The genus term is extremely broad and encompasses both the expression and down-regulation of any cell surface marker, cytokine, protein, DNA, RNA or other factor associated with the stimulation of a particular T cell, including as yet undiscovered proteins and factors. It also includes the determination of T cell activation by any method, including as yet unknown methods. In addition, a sufficient description of a representative

number of marker species, with relevant identifying characteristics other than measuring T cell activation is not disclosed. Therefore, there is insufficient description in the specification to support the recited term.

Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 27, 2007

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